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podsekretar

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Ločitev olanzapina od sorodnih nečistoč

6. Podatki o zahtevani prednostni pravici in podlagi zanjo:

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- ☐ prijava je za patent s skrajšanim trajanjem
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8. Izjava:

- ☐ izjava o skupnem predstavniku:

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- ☒ opis izuma, ki ima __19__ strani 2x
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MINISTRSTVO ZA GOSPODARSTVO
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Alenka Košak
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SEPARATION OF OLANZAPINE FROM ITS HIGHLY RELATED IMPURITIES

Technical field

The invention belongs to the field of organic chemistry and relates to a new effective process for the preparation of pure 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (olanzapine) by removing similar related compounds via preparation of acid addition salts of olanzapine with different organic acids. Effective procedures for the preparation of pure and well characterized acid addition salts of the titled molecule and the transformation thereof into a pharmaceutically acceptable final product are found. This method is available for the purification of the titled compound prepared by various manners. 2-Methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine is used for treatment of various mental diseases with the generic name olanzapine.

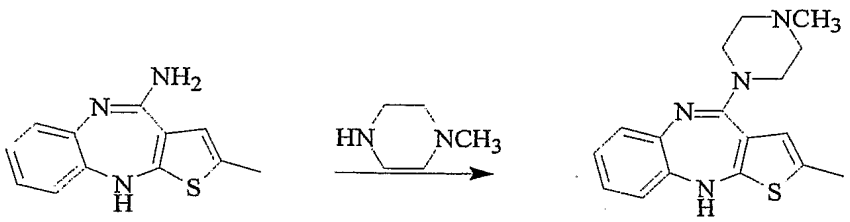
Background of the invention

Olanzapine (2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine) was first disclosed in British patent GB 1,533,235 in a wider group of potentially active molecules.

Patent EP 0454436 discloses a one-step process for olanzapine preparation. One of the described procedures consists of a reaction of the 4-amino-2-methyl-10*H*-thieno[2,3-*b*][1,5]benzodiazepine hydrochloride with N-methylpiperazine in an organic solvent such as anisole, toluene, dimethylformamide or dimethyl sulfoxide, preferably at a temperature from 100 to 150 °C to yield olanzapine (Scheme 1). The same patent also predicted potential formation of acid addition salts of olanzapine and its possible use in purification of olanzapine and in pharmaceutical use but none

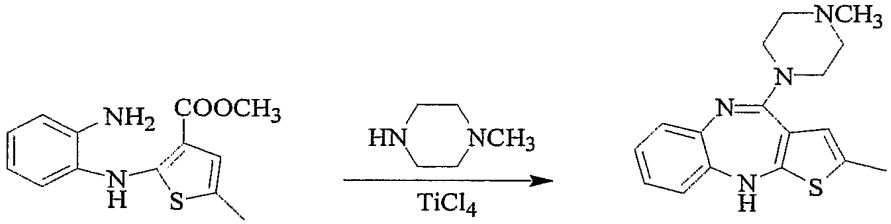
of these acid addition salts were prepared and characterized and no use of any acid addition salt was disclosed.

Scheme 1



Another process disclosed in patent EP 0454436 is a reaction of N-methylpiperazine with methyl-2-(2-aminoanilino)-5-methylthiophene-3-carboxylate in the presence of titanium tetrachloride (Scheme 2).

Scheme 2



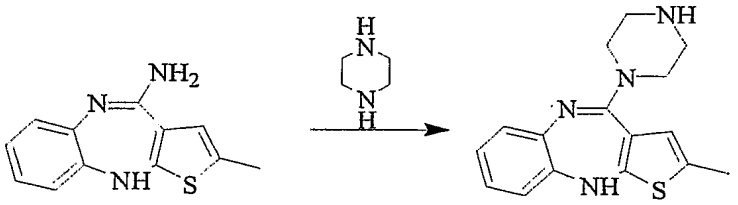
One disadvantage of the prior art process is the use of solvents that have a high boiling point and are difficult for removing from the reaction mixture, such as toluene, dimethylformamide, dimethyl sulfoxide. Another disadvantage is dark colour of the final product which has to be removed by repeated crystallizations.

In the patent application WO 04000847, preparation of olanzapine from 4-amino-2-methyl-10*H*-thieno[2,3-*b*][1,5]benzodiazepine via N-desmethylolanzapine with reductive N-methylation (formaldehyde / metal boron hydride) is disclosed. This patent also covered methylation with methyl iodide in methanol and usage of potassium carbonate as a base. Disadvantages of processes disclosed therein are low yields and bad quality of the final product.

Reaction of 4-amino-2-methyl-10*H*-thieno[2,3-*b*][1,5]benzodiazepine hydrochloride with piperazine to produce N-desmethylolanzapine (Scheme 3) was published in

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 1, pp. 25–30, 1997. A mixture of dimethyl sulfoxide / toluene = 1 / 4 was used. Disadvantage of the reaction at a higher temperature in this mixture is dark coloured product.

Scheme 3:



It is well known to a skilled person that most chemical reactions are not completely finished, may be reversible or are driven simultaneously with some other parallel reactions. Starting materials or side reaction products are usually found as impurities in the isolated main product which should therefore be further purified. The simplest way of purification includes various recrystallization and precipitation procedures which are usually less effective if the impurities have physico-chemical properties very similar to the main product.

Thus in the case of preparation of olanzapine by the process disclosed in EP 0454436, the starting material, 4-amino-2-methyl-10H-thieno[2,3-b][1,5]-benzodiazepine, is found as an impurity. In the case of preparation of olanzapine by a two-step process, the presence of 4-amino-2-methyl-10H-thieno[2,3-b][1,5]-benzodiazepine is not critical but various other similar compounds could be found as impurities, such as 4-(4-formylpiperazinyl)-2-methyl-10H-thieno[2,3-b][1,5]-benzodiazepine and N-desmethylolanzapine. For all these impurities that have a thienobenzodiazepine ring system as a part of the molecule skeleton and because it represents a great part of molecule, said ring system is crucial for similarity of physico-chemical properties of said impurities compared to olanzapine.

In the patent SI P 200400079 a two-step process for the synthesis of 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine (olanzapine) *via* a purified intermediate, 2-methyl-4-(1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzo diazepine, is disclosed.

We found that olanzapine cannot be effectively separated from its highly related impurities using repeated crystallization or precipitation methods.

Detailed description of the invention

The present invention provides a process for the purification of olanzapine via preparation of acid addition salts of olanzapine with organic acids. Crude olanzapine may enter into the purification process in an isolated form or as crude product obtained directly from the synthesis that includes various synthetic steps through the solutions, solvent extracts or evaporates. Purified olanzapine from the invented procedure could be finally prepared in various crystal forms, such as form I or form II.

It is known in the state of the art that formation of acid addition salts of a substance and crystallization thereof from a solution can successfully purify said substance from impurities which cannot form acid addition salts and also from impurities which can form such salts but the properties thereof differ in a great extent from the said substance. It was surprisingly found that olanzapine contaminated with highly related impurities can effectively be purified by transformation into an acid addition salts which were precipitated from the solvents with excellent purifying capacity. This is in contrast to olanzapine itself and some other olanzapine salts, particularly inorganic salts. We found that suitable organic acids that could be used for the preparation of olanzapine acid addition salts having capability for separation are carboxylic acids with at least one carboxylic group, such as oxalic, fumaric and benzoic acid, preferably oxalic acid, or sulfonic acids and the like. Moreover it was found, that N-desmethylolanzapine also precipitated from solvents in the form of an acid addition salt. But it was surprisingly found that derivatives of N-desmethylolanzapine, such as acetyl, do not precipitate from organic solvents as an acid addition salt. Said method of purification was very effective to ensure the level of any single impurity of pharmaceutical grade olanzapine below 0.1 % and the method was particularly important for removing N-desmethylolanzapine which can otherwise be very difficult for separating from olanzapine. The level of impurities decreased in an appreciable extent even if the level of impurities in crude olanzapine was high.

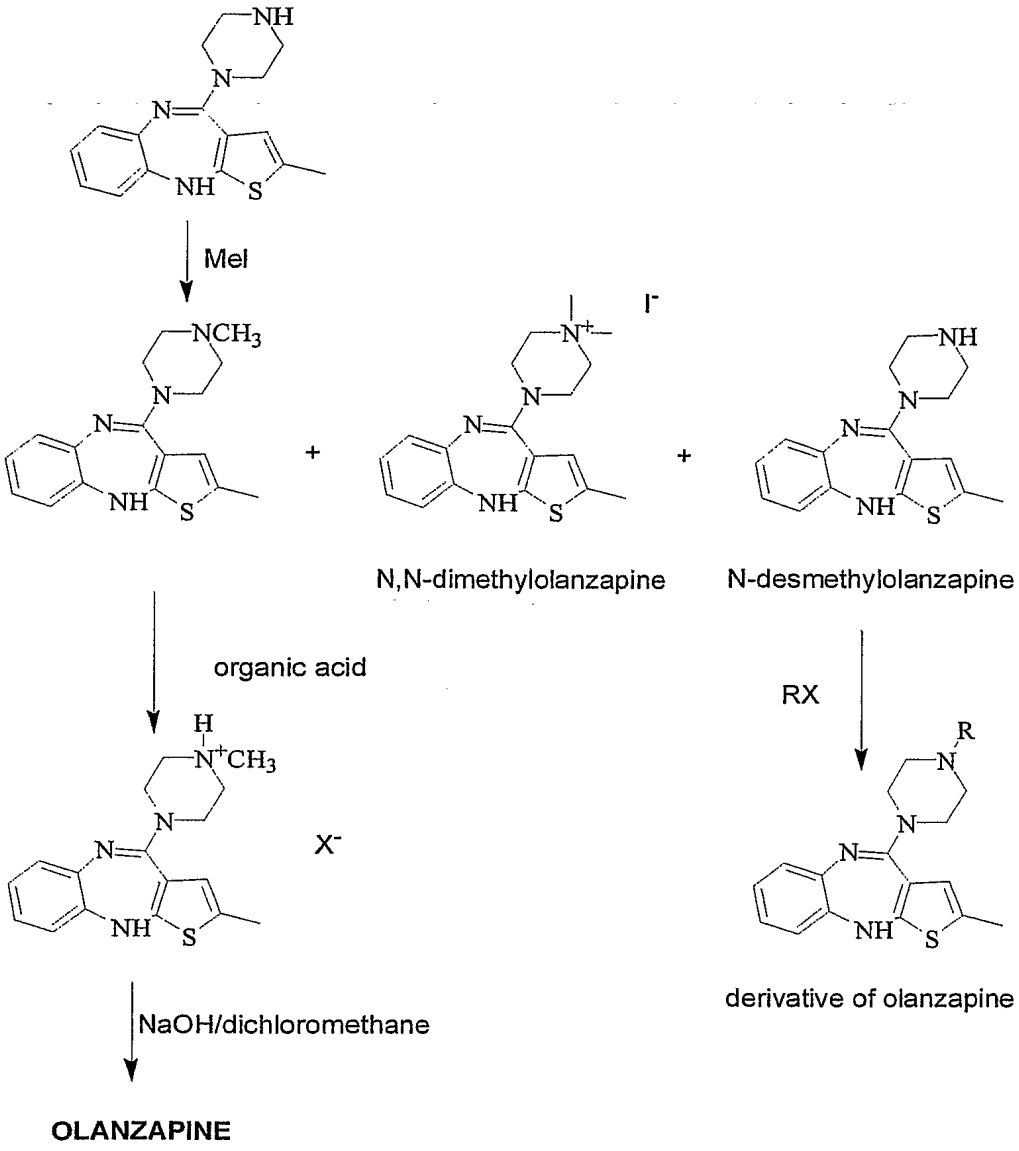
Another embodiment of the present invention is a process for producing olanzapine which comprises a reaction between piperazine and 4-amino-2-methyl-10H-thieno[2,3-b][1,5]-benzodiazepine in order to produce N-desmethylolanzapine and further methylation of N-desmethylolanzapine with a methylating agent, such as methyl iodide, dimethyl sulphate or trimethyl phosphate, to produce olanzapine of a pharmaceutical grade quality via an acid addition salt preparation.

Reaction of 4-amino-2-methyl-10*H*-thieno[2,3-*b*][1,5]benzodiazepine hydrochloride with piperazine is carried out in the presence of a high boiling solvent, preferably 1-butanol, 2-butanol, dimethyl sulfoxide, dimethylacetamide, dimethylformamide, xylene, toluene, ethylbenzene, anisole and the like, more preferably in mixtures of butanol:xylene = about 10:90 to about 90:10. The resulting N-desmethylolanzapine is precipitated from water. N-desmethylolanzapine is methylated with methyl iodide in a solvent, such as methylene chloride, tetrahydrofurane, diethylether and the like, either used alone or mixed with other solvents, preferred is a mixture of tetrahydrofurane with polar solvents. Such polar solvents are dipolar aprotic solvents, such as amides (dimethylformamide, dimethylacetamide, N-methylpyrrolidone), ureas (1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, 1, 3-dimethyl-2-imidazolidinone, tetramethylurea), dimethyl sulfoxide, sulfolane, acetone, acetonitrile and the like. Such mixtures of tetrahydrofurane and polar solvents are superior in ensuring a higher ratio of olanzapine versus non-methylated and dimethylated products (Scheme 4). Nevertheless N-desmethylolanzapine and N,N-dimethylolanzapine are the main impurities in this synthesis.

In order to obtain as little as possible of the dimethyl by-product, the reaction is controlled in such a way that 1-5 % of the starting compound (N-desmethylolanzapine) remains in the reaction mixture after the reaction is finished.

For removing this remaining N-desmethylolanzapine out of the reaction mixture, N-substituted derivative can be prepared from N-desmethylolanzapine. Reactants that could be used for said derivatization are chloroacetic acid, chloroethylamine, benzyl bromide, phthalic anhydride, acetic anhydride, and the like, shown as RX in Scheme 4.

Scheme 4:



For the reaction, different amines, such as dicyclohexylamine, diisopropylamine, triethylamine, diisopropylethylamine, diazabicyclooctane, ethylenediamine, isopropylamine, butylamine, diethylamine, dipropylamine, propylamine, dibutylamine and the like, and different inorganic bases, such as K_2CO_3, Na_2CO_3, NaOH, KOH, LiOH, $Ca(OH)_2$, NaH, and the like, can be used.

The resulting reaction mixture is extracted with organic solvents, such as diethyl ether, ethyl acetate or preferably chlorinated organic solvents, such as methylene chloride and chloroform. Organic phase is washed with water, followed by the

addition of RX (where RX is chloroacetic acid, chloroethylamine, benzyl bromide, phthalic anhydride or acetic anhydride, and the like) followed by the addition of an organic acid, such as sulfonic or carboxylic acid, preferably oxalic, fumaric and benzoic, and the like. Olanzapine acid addition salt is filtered off. It was surprisingly found that N-desmethylolanzapine derivatives precipitate as acid addition salts in a very little extent which means that separation from olanzapine is nearly 100 %. On the other hand, the N,N-dimethylolanzapine by-product was completely removed by the combination of effective washing with water in the extraction step and olanzapine acid addition salt formation.

Olanzapine acid addition salts can easily be transformed to pure olanzapine in crystal forms I or II by dissolving in water and adding a low boiling organic solvent, such as diethyl ether, methylene chloride, chloroform, ethyl acetate, preferably methylene chloride and the like, followed by the addition of a base, preferably inorganic bases such as ammonia, K_2CO_3, KOH, NaH, Na_2CO_3, LiOH, $Ca(OH)_2$ and the like, more preferably NaOH, to obtain a pH of about 7 – 11 preferably a pH of about 9 – 10. After the desired pH is obtained, the mixture is extracted with a low boiling organic solvent, such as diethyl ether, methylene chloride, chloroform, ethyl acetate, preferably methylene chloride and the like.

After the extraction, the residual organic solvent is partly removed by rotary evaporation and the residual mixture is cooled to about -20 to about 0 °C, preferably about -15 to about -5 °C and olanzapine crystal form I is precipitated.

In another embodiment the invention provides a process for the preparation of crystal form II by completely removing the organic solvent by rotary evaporation, followed by the addition of an organic solvent, preferably diethyl ether, acetonitrile, ethyl acetate, and the like.

Another embodiment of the present invention is a process for producing olanzapine crystal form I via olanzapine acid addition salts which comprises the reaction of N-methylpiperazine and 4-amino-2-methyl-10H-thieno[2,3-b][1,5]- benzodiazepine. The reaction is carried out in the presence of a high boiling solvent, preferably dimethyl sulfoxide, dimethylacetamide, butanol, dimethylformamide, toluene, xylene, ethylbenzene, anisole and the like at a temperature of about 80 – 150 °C, preferably from about 115 – 130 °C. The resulting olanzapine is extracted with an organic

solvent, preferably acetone, methylene chloride and chloroform, followed by the addition of an organic acid, such as carboxylic acid, for example oxalic, fumaric, benzoic acid, or sulfonic acid and the like. Olanzapine acid addition salt is filtered off, dissolved in water and extracted with an organic solvent, preferably acetone, methylene chloride and chloroform in basic conditions. Organic solvent is evaporated off and olanzapine crystal form I is precipitated.

Another embodiment of this invention is the recovery of mother liquors from any crystallization step of olanzapine base. Mother liquor is directly treated with an organic acid, such as carboxylic acid, for example oxalic, fumaric, benzoic acid, or sulfonic acid and the like, and precipitation of olanzapine acid addition salt takes place or mother liquid is first concentrated by evaporation of solvents and further diluted by other solvents being more suitable for acid addition salt purification, preferably by the addition of methylene chloride and methanol. This olanzapine acid addition salt can further be transformed to pure olanzapine.

Olanzapine manufactured by the process of the present invention is suitable for pharmaceutical use in any pharmaceutical formulation, e.g. for treatment of various medical conditions, particularly mental diseases and conditions..

The invention is illustrated but not limited by the following examples.

Abbreviations:

DMAC	Dimethylacetamide
DMF	Dimethylformamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	Dimethyl sulfoxide
NMP	N-methylpyrrolidone

Preparation of olanzapine acid addition salts from an isolated olanzapine

Preparation of olanzapine oxalate

Example 1

To a solution of 0.45 g of olanzapine in 18 ml of DMI, a solution of 0.26 g of oxalic acid in 0.5 ml of DMI is added. After 10 minutes of stirring at 25 °C, crystallization begins. The suspension is stirred for one hour at 25 °C and then stirring is continued for one hour on an ice bath. Then the product is isolated by filtration. The product is washed with 25 ml of methylene chloride and dried for two hours at 50 °C in vacuo.

Yield: 0.72 g of yellow, crystalline powder.

mp: 235 °C

^{1}H NMR: (300.1 MHz, DMSO-d6)

δ = 2.275 (s, 3 H, CH_3), 2.625 (s, 4 H, $NC\underline{H_3}CO$), 2,754 (s. 3 H, CH_3), 3.141(4 H, piperazinyl-H,), 3.193 (s, 4 H, $C\underline{H_2}NCH_3CO$) 3.582 (4 H, piperazinyl-H), 6.436 (s, 1 H, thiophenyl-H), 6.579 (s, 4 H, HC=CH), 6.651 (s, 6.74 (m, 1 H, Ar), 6.909 (m, 3 H, Ar), 7.954 (s,1 H, NH), 9.301 (broad, 3 H, NH, OH).

Example 2

To a solution of 0.45 g of olanzapine in 18 ml of DMI, a solution of 0.26 g of oxalic acid in 0.5 ml of DMAC is added. After 10 minutes of stirring at 25 °C, crystallization starts. The suspension is stirred for one hour at 25 °C and then stirring is continued for one hour on an ice bath. Then the product is isolated by filtration. The product is washed with 25 ml of methylene chloride and dried for two hours at 50 °C in vacuo.

Yield: 0.75 g of yellow, crystalline powder

mp: 221 °C

^{1}H NMR: (300.1 MHz, DMSO-d6)

δ = 1,955 (s, 3 H, CH_3CON), (s, 3 H, 2.275 (s, 3 H, CH_3), 2.625 (s, 4 H, $NC\underline{H_3}CO$), 2,707 and 2, 754 (2 s, 6 H, CH_3, $CONCH_3$), 2,940 (s, 3 H, $CONCH_3$), 3.180 (4 H, piperazinyl-H,), 3.583 (4 H, piperazinyl-H), 6.416 (s, 1 H, thiophenyl-H), 6.416 (m, 1 H, Ar), 6.579 (m, 3 H, Ar), 7.846 (s,1 H, NH), 8.787 (broad, 3 H, NH, OH).

Example 3

To a suspension of 0.45 g of olanzapine in 18 ml of acetonitrile, a solution of 0.26 g of oxalic acid in 2 ml of acetonitrile is added. The suspension is stirred for one hour at 25 °C and then the stirring is continued for one hour on an ice bath. Then the product

is isolated by filtration, washed with 25 ml of acetonitrile and dried for 15 hours at 60 °C in vacuo.

Yield: 0.58 g of yellow, crystalline powder

mp:	235 °C
Assay:	73.5 %
Oxalic acid:	24.3 %
Acetonitrile:	3 mol %

Example 4

To a suspension of 0.45 g of olanzapine in 18 ml of ethanol, a solution of 0.26 g of oxalic acid in 0.5 ml of ethanol is added. After the addition of the solution of oxalic acid, the products start to crystallize from the solution. The suspension is stirred for one hour at 25 °C and then stirring is continued for one hour on an ice bath. Then the product is isolated by filtration. The product is washed with 25 ml of ethanol and dried for two hours at 60 °C in vacuo.

Yield: 0.56 g of yellow, crystalline powder

mp:	224 °C
Assay:	75.8 %
Oxalic acid:	24.0 %

Example 5

To a solution of 0.45 g of olanzapine in 18 ml of isopropanol, a solution of 0.26 g of oxalic acid in 2 ml of isopropanol is added. After the addition of the solution of oxalic acid, crystallization starts. The suspension is stirred for one hour at 25 °C and then stirring is continued for one hour on an ice bath. Then the product is isolated by filtration, washed with 25 ml of isopropanol and dried for 15 hours at 60 °C in vacuo.

Yield: 0.60 g of yellow, crystalline powder

mp:	230 °C
Assay:	65.18 %
Oxalic acid:	21.5 %
Isopropanol:	94 mol %

Preparation of olanzapine fumarate

Example 6

To a solution of 0.45 g of olanzapine in 18 ml of isopropanol, 0.26 g of fumaric acid is added. The suspension formed is stirred for one hour at 25 °C and then stirring is continued for one hour on an ice bath. Then the product is isolated by filtration. The product is washed with 25 ml of isopropanol and dried for 15 hours at 60 °C in vacuo.

Yield: 0.55 g of yellow, crystalline powder

mp:	231 °C
Assay:	75.5 %
Fumaric acid:	17.3 %
Isopropanol:	50 mol %

^{1}H NMR: (300.1 MHz, DMSO-d6).

δ = 2.334 (s, 3 H, CH_3), 2.443 (s, 3 H, CH_3), 2.729 (4 H, piperazinyl-H), 3.434 (4H, piperazinyl-H), 5.753 (s, 1.36 H, CH_2Cl_2), 6.346 (s, 1 H, thiophenyl-H), 6.579 (s, 4 H, COHC=CHCO), 6.651 (s, 6.643 (m, 1 H, ArH), 6.834 (m, 3 H, ArH), 7.634 (s,1 H, NH).

Preparation of olanzapine benzoate

Example 7:

To a solution of 0.45 g of olanzapine in 18 ml of acetone, 0.26 g of benzoic acid is added. The suspension formed is stirred for one hour at 25 °C and then stirring is continued for one hour on an ice bath. Then the product is isolated by filtration. The product is washed with 25 ml of acetone and dried for 15 hours at 60 °C in vacuo.

Yield: 0.60 g of yellow, crystalline powder.

mp:	205 °C
Assay:	70.0 %
Benzoic acid:	26.1 %
Acetone:	5.2 mol %

^{1}H NMR: (300.1 MHz, DMSO-d6)

δ = 2.334 (s, 3 H, CH_3), 2.443 (s, 3 H, CH_3), 2.729 (4 H, piperazinyl-H), 3.434 (4 H, piperazinyl-H), 6.365 (s, 1 H, thiophenyl-H), 6.579 (s, 4 H, COHC=CHCO), 6.651 (s, 6.643 (m, 1 H, ArH), 6.834 (m, 3 H, ArH), 7.686 (s,1 H, NH)

Preparation of olanzapine addition salts directly from the process of synthesis

Preparation of olanzapine oxalate

Example 8

A solution of 12.0 g of N-desmethylolanzapine in a mixture of 180 ml of THF and 120 ml of 1,3-dimethylimidazolinone (DMI) is cooled to approx. -20 °C. At -19 °C to the solution, 8.19 g of diisopropylamine and afterwards 13.7 g of methyl iodide are added. After stirring the reaction mixture for 45 minutes at -19 °C, 6.4 ml of concentrated hydrochloric acid and a solution of 6.36 g of thiourea in 50 ml of water are added and the reaction mixture is stirred for 15 minutes at 20 °C.

After the addition of 50 ml of water, the mixture is evaporated at a bath temperature of 35 °C and at 50 - 60 mbar to a volume of cca. 160 ml. Then 400 ml of water and 120 ml of methylene chloride are added and pH is adjusted to 2.0 with 6 N HCl. After separation of the phases, the water phase is washed twice with 120 ml of methylene chloride. To the water phase, 180 ml of methylene chloride are added and pH is adjusted to 9.0 by the addition of 1 N NaOH. After 5 minutes of stirring, the phases are separated and the alkaline water phase is extracted twice with 90 ml of methylene chloride. The organic phases are combined and the mixture is diluted with 37.5 of methanol and under stirring a solution of 7.46 g of oxalic acid in 10.5 ml of methanol is added within 15 minutes. The resulting suspension is stirred for about 1 hour at approx. 20 °C and afterwards 1 hour at approx. 0 °C.

The product is isolated by filtration, washed with 100 ml of methylene chloride and dried for 2 hours at 50 °C in vacuo.

Yield: 15.15 g (69.2 %)

mp: 228 °C

Assay: 54.1 %

HPLC-Purity: 98.2 area %

N-desmethylolanzapine: 0.95 area %

Oxalic acid: 31.6 %

DMI: 6 mol %

Methylene chloride: 0.5 mol %

Example 9

A solution of 12.0 g of N-desmethylolanzapine in 240 ml of dimethylacetamide (DMAC) is cooled to approx. -20 °C. At -20 °C 8.19 g of diisopropylamine are added to the solution and afterwards 7.19 g of methyl iodide are added. After stirring the

reaction mixture for 95 minutes at -20 °C, 6.4 ml of concentrated hydrochloric acid and a solution of 6.36 g of thiourea in 50 ml of water are added and the reaction mixture is stirred for 15 minutes at 20 °C. Then 400 ml of water and 120 ml of methylene chloride are added and the pH is adjusted to 2.0 with 6 N HCl. After separation of the phases, the water phase is washed twice with 140 ml of methylene chloride. To the water phase, 180 ml of methylene chloride are added and pH is adjusted to 9.0 by the addition of 1 N NaOH. After 5 minutes of stirring, the phases are separated and the alkaline water phase is extracted twice with 90 ml of methylene chloride. The organic phases are combined and 380 mg of acetic anhydride is added and the mixture is stirred for 5 minutes. Then the mixture is diluted with 37.5 of methanol and under stirring, a solution of 7.46 g of oxalic acid in 10.5 ml of methanol is added within 15 minutes. The resulting suspension is stirred for about 1 hour at approx. 20 °C and afterwards 1 hour at approx. 0 °C. The product is isolated by filtration, washed with 100 ml of methylene chloride and dried for 15 hours at 25 °C in vacuo.

Yield: 13.76 g (72.0 %)

mp: 233 °C

Assay: 59.4 %

HPLC-Purity: 98.3 area %

N-desmethylolanzapine: 0.15 area %

Oxalic acid: 29.1 %

Methylene chloride: 69.9 mol %

DMAC: 2.3 mol %

Example 10

A solution of 12.0 g of N-desmethylolanzapine in 240 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-1,3-pyrimidinone is cooled to approx. -20 °C. At -20 °C 8.19 g of diisopropylamine are added to the solution and afterwards 7.57 g of methyl iodide are added. After stirring the reaction mixture for 60 minutes at -20 °C, 7.2 ml of concentrated hydrochloric acid and a solution of 6.36 g of thiourea in 50 ml of water are added and the reaction mixture is heated to 20 °C and stirred for 5 minutes at the same temperature. Then 400 ml of water and 120 ml of methylene chloride are added and pH is adjusted to 2.0 with 6 N HCl. After separation of the layers, the water layer is washed twice with 120 ml of methylene chloride. To the water phase

180 ml of methylene chloride are added and pH is adjusted to 9.0 by the addition of 1 N NaOH. After 5 minutes of stirring, the layers are separated and the alkaline water layer is extracted twice with 90 ml of methylene chloride. The organic layers are combined and 380 mg of acetic anhydride are added and the mixture is stirred for 5 minutes. Then the solvent is evaporated in vacuo and the oily residue is dissolved in a mixture of 360 ml of methylene chloride, 37.5 ml of methanol and 0.72 ml of water. To this solution seeds of olanzapine crystal form I are added and while stirring a solution of 7.71 g of oxalic acid in 10.5 ml of methanol within 20 minutes is added. The resulting suspension is stirred for about 1 hour at approx. 25 °C and afterwards 1 hour at approx. 0 °C. The product is isolated by filtration, washed with 100 ml of methylene chloride and dried for 15 hours at 60 °C in vacuo.

Yield: 14.8 g (82.4 %) of yellow, crystalline powder

mp: 229 °C

Assay: 64.1 %

HPLC-Purity: 99.5 area %

N-desmethylolanzapine: < 0.1 area %

Oxalic acid: 32.4 %

Methylene chloride: 10.4 mol % (drying 24 h at 50 °C)

DMPU: 0.5 mol %

Example 11

A mixture of 30.0 g of 4-amino-2-methyl-10*H*-thieno[2,3-b][1,5]-benzodiazepine hydrochloride and 81 ml of N-methylpiperazine in 186 ml of DMSO is heated to 117 °C. After 17 hours of stirring and bubbling nitrogen through the mixture at this temperature, the resulting solution is cooled to room temperature (R.T.) and then 570 ml of methylene chloride and 570 ml of water are added. After stirring the mixture for 5 minutes, the layers are separated. The alkaline water layer is extracted with 300 ml of methylene chloride. To the combined organic layers, 250 ml of water are added and pH is adjusted to 2.0 by the addition of 6 M HCl. After separating the layers, the organic layer is extracted twice with 90 ml of water. The combined acidic water layers are treated with 4.5 g of charcoal. After 5 minutes of stirring, charcoal is filtered off and the cake is washed with 100 ml of water. Filtrate and wash water are combined and after adding of 950 ml of methylene chloride, pH is adjusted to 9.0 by the addition of 5 M NaOH. After separating the layers, the alkaline water layer is

extracted with 125 ml of methylene chloride. The organic layers are combined and evaporated in vacuo. The oily residue is dissolved in a mixture of 1075 ml of methylene chloride, 140 ml of methanol and 3.6 ml of water and heated to about 29 - 30 °C. After adding seeds of olanzapine crystal form I to the solution, a solution of 18.7 g of oxalic acid in 27 ml of methanol is added within 30 minutes. The resulting suspension is stirred for about 1 hour at approx. 25 °C and afterwards 2 hours at approx. 0 °C. The product is isolated by filtration, washed with 150 ml of methylene chloride and dried for 6 hours at 60 °C in vacuo.

Yield: 43.3 g (82.2 %) of yellow, crystalline powder
mp: 224 °C
Assay: 62.7 %
HPLC-Purity: 99.6 area %
Oxalic acid: 26.1 %
Methylene chloride: 22 mol %

Preparation of olanzapine fumarate

Example 12

To the solution of olanzapine (obtained from 12.0 g of starting N-desmethylolanzapine, according to example 16) in the mixture of 360 ml of methylene chloride, 37.5 of methanol and 0.72 mg of water, seeds of olanzapine crystal form I and 0.96 g of fumaric acid are added. The resulting suspension is stirred for about 1 hour at 25 °C and afterwards 2 hours at approx. 0 °C. The product is isolated by filtration, washed with 150 ml of methylene chloride and dried for 6 hours at 60 °C in vacuo.

Yield: 11.4 g (65.7 %) of light yellow, crystalline powder
mp: 217 °C
Assay: 65.7 %
HPLC-Purity: 97.8 area %
N-desmethylolanzapine: 0.15 area %
Fumaric acid: 23.2 %
Methylene chloride: 48 mol %

Example 13

A solution of olanzapine prepared from 30.0 g of 4-amino-2-methyl-10*H*-thieno[2,3-b][1,5]-benozodiazepine hydrochloride and 81 ml of N-methylpiperazine in 186 ml of DMSO according to example 5, is heated to 29 - 30 °C. At this temperature seeds of olanzapine crystal form I and 14.4 g of fumaric acid are added. The resulting suspension is stirred for about 1 hour at 29 - 30 °C and afterwards 2 hours at approx. 0 °C. The product is isolated by filtration, washed with 150 ml of methylene chloride and dried for 6 hours at 60 °C in vacuo.

Yield: 41.9 g (85.2 %) of light yellow, crystalline powder
mp: 217 °C
Assay: 68.5 %
HPLC-Purity: 99.7 area %
Fumaric acid: 23.0 %
Methylene chloride: 48 mol %

Preparation of olanzapine crystal form I from olanzapine oxalate

Example 14

7.40 g of olanzapine oxalate are dissolved in 75 ml of water and the pH of the solution is adjusted to 2.0 by the addition of 6 N HCl. To the resulting clear solution of olanzapine oxalate, 0.75 g of charcoal is added. After stirring for 5 minutes, charcoal is filtered off and the cake is washed with 50 ml of water. Filtrate and wash water are combined and after the addition of 125 ml of methylene chloride, pH of combined mixture is adjusted to 9.0 by the addition of 1 N NaOH. After stirring for 5 minutes, the layers are separated and the water phase is extracted with 25 ml of methylene chloride. The organic layers are combined and after drying with sodium carbonate, the solution is concentrated in vacuo to a volume of 27 ml. Then the concentrated solution is heated to the reflux temperature at a normal pressure and after adding seeds of olanzapine crystal form I, the solution is immediately cooled on an ice bath. Adding said seeds is continued until olanzapine begins to crystallize. The resulting suspension is stirred for 15 minutes on an ice bath and then for 15 minutes at about -20 °C. Then olanzapine is isolated by filtration. The cake is washed with 3 ml of methylene chloride and cooled to -20 °C. The product is dried for two days at 25 °C in vacuo.

Yield: 3.63 g (72.6 %)

HPLC-Purity: 99.9 %

IR - identical with olanzapine crystal form I reference substance

XRD - identical with olanzapine crystal form I reference substance

Preparation of olanzapine crystal form II from olanzapine oxalate

Example 15

7.40 g of olanzapine oxalate are dissolved in 75 ml of water and pH of the solution is adjusted to 2.0 by the addition of 6 N HCl. To the resulting clear solution of olanzapine oxalate, 0.75 g of charcoal is added. After stirring for 5 minutes, charcoal is filtered off and the cake is washed with 50 ml of water.

Filtrate and wash water are combined and after the addition of 125 ml of methylene chloride, pH of combined mixture is adjusted to 8 - 10 by the addition of 1 N NaOH. After stirring for 5 minutes, the layers are separated and the water phase is extracted with 25 ml of methylene chloride. The organic layers are combined and the methylene chloride is evaporated. Then ethyl acetate is added and olanzapine starts to crystallize. The resulting suspension is stirred for 15 minutes on an ice bath. Then olanzapine is isolated by filtration. The product is dried for two hours at 60 °C in vacuo.

Yield: 3.4 g

HPLC-Purity: 99.9 %

IR - identical with olanzapine crystal form II reference substance

XRD - identical with olanzapine crystal form II reference substance

Preparation of olanzapine from N-desmethylolanzapine

Example 16

A solution of 20.0 g of N-desmethylolanzapine in a mixture of 150 ml of THF and 60 ml of DMAC is cooled to approx. -15 °C. At -15 °C to the reaction mixture, 20 ml of diisopropylamine are added and afterwards 6 g of methyl iodide in 30 ml of THF are added within 30 - 40 minutes. After stirring the reaction mixture for another 60 minutes at -5 to -10 °C, 16 ml of concentrated hydrochloric acid in 100 ml of water and a solution of 3.3 g of thiourea in 100 ml of water are added and the reaction mixture is stirred for 15 minutes at 20 °C.

The THF is evaporated at a bath temperature of 35 °C and at a pressure of 50 - 60 mbar to a volume of cca. 200 ml. Then 300 ml of methylene chloride are added and pH is adjusted to 8.5 - 10 with 40 % NaOH. After separation of the phases, the water phase is washed twice with 100 ml of methylene chloride. Organic phases are combined and washed three times with 100 ml of water. The organic phases are combined, 0.5 ml of acetic anhydride is added and the mixture is stirred for 5 minutes. A solution of 10.34 g of oxalic acid dihydrate in 40 ml of methanol is added within 15 minutes. The resulting suspension is stirred for about 1 hour at approx. 20 °C and afterwards 1 hour at approx. 0 °C. The product is isolated by filtration, washed with 100 ml of methylene chloride and dried for 2 hours at 50 °C in vacuo.
Yield: 25.1 g.

25 g of olanzapine oxalate are dissolved in 250 ml of water and pH of the solution is adjusted to 2.0 by the addition of 6 N HCl. To the resulting clear solution of olanzapine oxalate, 2.5 g of charcoal is added. After stirring for 5 minutes, charcoal is filtered off and the cake is washed with 50 ml of water. Filtrate and wash water are combined and after the addition of 300 ml of methylene chloride, pH is adjusted to 9 - 10 by the addition of 1 N NaOH. After stirring for 5 minutes, the layers are separated and the water phase is extracted with 50 ml of methylene chloride. The organic layers are combined and the solution is concentrated in vacuo to a volume of 50 ml. Then the concentrated solution is heated to reflux temperature at a normal pressure and after adding seeds of olanzapine crystal form I, the solution is immediately cooled on an ice bath. Adding said seeds is continued until olanzapine starts to crystallize. The resulting suspension is stirred for 15 minutes on an ice bath and then for 15 minutes at -20 °C. Then olanzapine is isolated by filtration. The cake is washed with 10 ml of methylene chloride and cooled to -20 °C. The product is dried for four hours at 80 °C in vacuo.
Yield: 11.5 g

Table 1 shows the analytical results of the intermediate olanzapine oxalate and the final product olanzapine prepared according to the process described in Example 16

	olanzapine oxalate	olanzapine
HPLC-purity	98.3 area %	99.8 area %

m.p.	228 °C	191 °C
N-desmethylolanzapine	0.05 area %	0.03 area %
N,N-dimethylolanzapine	1.25 area %	0.03 area %
acetylolanzapine	0.26 area %	0.06 area %

IR - identical with olanzapine crystal form I reference substance

XRD - identical with olanzapine crystal form I reference substance

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CLAIMS

1. A process for the preparation of olanzapine in the form of an acid addition salt with an organic acid characterized in that olanzapine and the corresponding organic acid are mixed together in a solvent or a mixture of solvents and the acid addition salt is precipitated and isolated by separation of crystals.

2. The process for the preparation of olanzapine acid addition salt according to claim 1 wherein said organic acid is selected from a group of oxalic acid, fumaric acid and benzoic acid.

3. The process for the preparation of olanzapine in the form of an acid addition salt according to claims 1 and 2 wherein said solvent comprises methanol.

4. The process for the preparation of olanzapine in the form of an acid addition salt according to claims 1 to 3 wherein olanzapine and said acid are mixed in a solvent mixture comprising methanol and methylene chloride.

5. The process for the preparation of olanzapine in the form of an acid addition salt with an organic acid according to claims 1-4 wherein:
   a) 2-methyl-4-amino-10H-thieno[2,3-b][1,5]benzodiazepine is reacted with methyl piperazine in the reaction mixture to yield olanzapine
   b) the obtained reaction mixture is diluted with water
   c) the obtained reaction mixture with olanzapine is extracted with an organic solvent
   d) the organic solvent is evaporated and the residue is diluted with the second solvent to obtain the solution
   e) an organic acid is added to the solution to precipitate the acid addition salt
   f) the precipitated acid addition salt is isolated by separation of crystals.

6. The process for the preparation of olanzapine in the form of an acid addition salt with an organic acid according to claim 5 wherein said organic solvent is a chlorinated solvent.

7. The process for the preparation of olanzapine in the form of an acid addition salt with an organic acid according to claims 5 and 6 wherein said chlorinated solvent is methylene chloride and said second solvent is methanol.

8. The process for the preparation of olanzapine in the form of an acid addition salt with an organic acid according to claims 1-4 wherein:
   a) 2-methyl-4-piperazinyl-10H-thieno[2,3-b][1,5]benzodiazepine is reacted with a methylating agent
   b) the obtained reaction mixture is diluted with water and acidified with an acid
   c) to the reaction mixture, organic solvent is added and the phases are separated
   d) the obtained water phase is neutralized and olanzapine is extracted with an organic solvent to obtain the organic solvent phase
   e) optionally the obtained organic solvent phase is evaporated and the residue is diluted with the second solvent
   f) an organic acid is added either to the diluted solution or directly to the olanzapine extract from said extraction in step d
   g) the precipitated acid addition salt is isolated by separation of the crystals.

9. The process for the preparation of olanzapine in the form of an acid addition salt with an organic acid, according to claim 8 wherein said organic solvent is a chlorinated solvent.

10. The process for the preparation of olanzapine in the form of an acid addition salt with an organic acid, according to claims 8 and 9 wherein said chlorinated solvent is methylene chloride and said second solvent is methanol.

11. The process for the preparation of olanzapine in the form of an acid addition salt with an organic acid according to claim 8-10 wherein said methylating agent is methyl iodide.

12. A process for the preparation of olanzapine characterized in that it is prepared from an acid addition salt thereof and by recovering olanzapine from the said salt.

13. The process for the preparation of olanzapine from an acid addition salt thereof according to claim 12 characterized in that it comprises the steps of:
    a) dissolving the acid addition salt of olanzapine in water
    b) adjusting pH of the obtained solution to about 8-10
    c) extracting olanzapine from the water phase to organic solvent phase
    d) isolating the final product from organic solvent phase by concentrating the solution and separation of the crystals.

14. A process for the purification of olanzapine characterized in that it is prepared by transforming it to the form of an acid addition salt thereof and recovering olanzapine from the said salt.

15. The process for the preparation of olanzapine crystal form I from an acid addition salt thereof according to claims 12-14 wherein the crystals are isolated from an organic solvent.

16. The process for the preparation of olanzapine crystal form I from an acid addition salt thereof according to claim 15 wherein said organic solvent is methylene chloride.

17. The process for the preparation of olanzapine crystal form II from an acid addition salt thereof according to claims 12-14 wherein the crystals are isolated from one or more solvents from the group of ethyl acetate, diethyl ether and acetonitrile.

18. A process for the preparation of a derivative of N-desmethylolanzapine characterized in that it comprises an addition of a chlorinated organic acid or an anhydride of organic acids.

19. The process for the preparation of a derivative of N-desmethylolanzapine according to claim 19 wherein said anhydride is acetic anhydride or phthalic anhydride.

20. Olanzapine prepared from N-desmethylolanzapine by methylation characterized in that N-desmethylolanzapine content in the final product of olanzapine is less than 0.1 %.

21. A process for the preparation of olanzapine acid addition salt characterized in that it comprises treatment of mother liquor obtained from isolation of final olanzapine with an organic acid.

22. Olanzapine in a form of an acid addition salt.

23. Oxalic acid addition salt of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine.

24. Fumaric acid addition salt of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine.

25. Benzoic acid addition salt of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine.

26. Use of organic acids in the process of preparation of olanzapine characterized in that olanzapine is purified via formation of an acid addition salt.

27. A pharmaceutical composition comprising 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine characterized in that it was prepared from an acid addition salt thereof according to the claims 1-17 and 20-21.

28. The use of olanzapine characterized in that it is prepared by the processes from claims 1-17 and 20-21 for the preparation of the medicament for the treatment of different mental diseases and conditions.

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Abstract

The invention belongs to the field of organic chemistry and relates to a new effective process for the preparation of pure 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (olanzapine) by removing similar related compounds via preparation of acid addition salts thereof with different organic acids. Effective procedures for the preparation of pure and well characterized acid addition salts of the titled molecule and the transformation of said salts into the pharmaceutically acceptable final product are found. This method is applicable for the purification of the titled compound.